HFD-613

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-709/S-030

JUN 3 1998

Bristol-Myers Squibb Company
Attention: Joseph A. Linkewich, Pharm.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Linkewich:

Please refer to your November 27, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Capozide (captopril/ hydrochlorothiazide) 25/15, 50/15, 25/25 and 50/25 mg Tablets.

We acknowledge receipt of your submission dated April 8, 1998.

The supplemental application provides for final printed labeling revised as follows:

PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility: This subsection has been revised to include the following three paragraphs before the captopril subsection:

> Carcinogenicity and fertility studies have not been conducted with CAPOZIDE, however, in animals they have been conducted with the individual components as noted below. Mutagenicity studies indicate that captopril in a 2:1 combination with hydrochlorothiazide was not mutagenic or clastogenic, with or without metabolic activation, in the following in vitro assays:
> 1) Ames reverse-mutation in Salmonella; 2) forward mutation study in Saccharomyces pombe; 3) mitotic gene conversion test in Saccharomyces cerevisiae; and 4) sister-chromatid-exchange study in human lymphocytes.
>
> In a cytogenetics study using human lymphocytes, there were no increases in chromosomal abnormalities without metabolic activation, nor with metabolic activation at 28 hours post-treatment. A statistically significant increase was found at 22 hours with metabolic activation at the three concentrations tested (captopril/hydrochlorothiazide in a 2:1 combination at 5, 25, 50 mcg/mL total weight); however, there was no dose response, and the difference is probably attributable to the unusual absence of any abnormalities in the negative-control cultures in this test.

In an oral micronucleus study in mice, the captopril/ hydrochlorothiazide combination (2:1 mixture at 2500 mg/kg total weight) was not genotoxic.

In addition, minor changes that would ordinarily be described in the NDA annual report are included:

The logo and signature were changed to “Bristol-Myers Squibb Company” and “Bristol-Myers Squibb Company, Princeton, NJ 08543 USA.”

“CAPOZIDE (captopril-hydrochlorothiazide tablets)” was changed to “CAPOZIDE (captopril-hydrochlorothiazide tablets, USP).”

Section cross-reference statements, e.g.,“(see **WARNINGS),** are now in bold text.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included with your submission dated April 8, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

We note that in telephone conversations on April 17 and 20, 1998 with Ms. Kathleen Jongedyk, at the time of your next printing you agreed to change the established name from “captopril-hydrochlorothiazide tablets, USP” to “captopril and hydrochlorothiazide, USP” to be identical to the USP monograph.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research